

PATENT COOPERATION TREATY

PCT

REC'D 15 APR 2005

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY
(Chapter II of the Patent Cooperation Treaty)

PCT

(PCT Article 36 and Rule 70)

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| Applicant's or agent's file reference 100914-1 WO | FOR FURTHER ACTION See Form PCT/IPEA/416 | |
| International application No. PCT/SE 2003/001956 | International filing date (day/month/year) 15.12.2003 | Priority date (day/month/year) 17.12.2002 |
| International Patent Classification (IPC) or national classification and IPC C07D 401/12, C07D 401/14, C07D 403/12, C07D 403/14, A61K 31/497, A61K 31/496, A61K 31/5377, A61P 25/00, A61P 3/10, A61P 5/48, A61P 15/18, A61P 17/14 | | |
| Applicant AstraZeneca AB et al | | |

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 9 sheets, including this cover sheet.

3. This report is also accompanied by ANNEXES, comprising:

- a. ☐ (sent to the applicant and to the International Bureau) a total of _____ sheets, as follows:
- ☐ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
- ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.

- b. ☐ (sent to the International Bureau only) a total of (indicate type and number of electronic carrier(s)) _____, containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

- ☒ Box No. I Basis of the report
- ☒ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☒ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☒ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

| | |
|---|---|
| Date of submission of the demand 18.06.2004 | Date of completion of this report 22.03.2005 |
| Name and mailing address of the IPEA/SE Patent- och registreringsverket Box 5055 S-102 42. STOCKHOLM | Authorized officer Eva Johansson/EÖ |
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Form PCT/IPEA/409 (cover sheet) (January 2004)

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.

PCT/SE 2003/001956

Box No. I Basis of the report

1. With regard to the language, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

☐ This report is based on a translation from the original language into the following language _____, which is the language of a translation furnished for the purposes of:

- ☐ international search (under Rules 12.3 and 23.1(b))
☐ publication of the international application (under Rule 12.4)
☐ international preliminary examination (under Rules 55.2 and/or 55.3)

2. With regard to the elements of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

☐ the international application as originally filed/furnished

☒ the description:

pages _____ as originally filed/furnished

pages* _____ received by this Authority on _____

pages* _____ received by this Authority on _____

☐ the claims:

pages _____ as originally filed/furnished

pages* _____ as amended (together with any statement) under Article 19

pages* _____ received by this Authority on _____

pages* _____ received by this Authority on _____

☐ the drawings:

pages _____ as originally filed/furnished

pages* _____ received by this Authority on _____

pages* _____ received by this Authority on _____

☐ a sequence listing and/or any related table(s) – see Supplemental Box Relating to Sequence Listing.

3. ☐ The amendments have resulted in the cancellation of:

☐ the description, pages _____

☐ the claims, Nos. _____

☐ the drawings, sheets/figs _____

☐ the sequence listing (*specify*): _____

☐ any table(s) related to the sequence listing (*specify*): _____

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).

☐ the description, pages _____

☐ the claims, Nos. _____

☐ the drawings, sheets/figs _____

☐ the sequence listing (*specify*): _____

☐ any table(s) related to the sequence listing (*specify*): _____

* If item 4 applies, some or all of those sheets may be marked "superseded."

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Box No. II Priority

1. ☐ This report has been established as if no priority had been claimed due to the failure to furnish within the prescribed time limit the requested:

☐ copy of the earlier application whose priority has been claimed (Rule 66.7(a)).
☐ translation of the earlier application whose priority has been claimed (Rule 66.7(b)).
2. ☐ This report has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rule 64.1). Thus for the purposes of this report, the international filing date indicated above is considered to be the relevant date.
3. Additional observations, if necessary:

The priority is considered valid.

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

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PCT/SE 2003/001956

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application☒ claims Nos. 11-16

because:

☒ the said international application, or the said claims Nos. 11-16
relate to the following subject matter which does not require an international preliminary examination (*specify*):

See PCT Rule 67.1.(iv).: Methods for treatment of the human or animal body by surgery or therapy, as well as diagnostic methods.

☒ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. 3, 5, 11
are so unclear that no meaningful opinion could be formed (*specify*):

The expression "conditions associated with glycogen synthase kinase-3" in claims 3, 5 and 11 is not clear and concise and does not comply with PCT Articles 5 and 6 as it defines the conditions by the mechanism behind the conditions and does not mention the specific conditions. It is therefore not clear

.../...

☐ the claims, or said claims Nos. _____ are so inadequately supported by the description that no meaningful opinion could be formed.☐ no international search report has been established for said claims Nos. _____☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form

☐ has not been furnished☐ does not comply with the standard

the computer readable form

☐ has not been furnished☐ does not comply with the standard☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in the Annex C-bis of the Administrative Instructions.☐ See Supplemental Box for further details.

Supplemental Box

In case the space in any of the preceding boxes is not sufficient.

Continuation of: Box III.2

which conditions are comprised by these claims. The search has been performed on the general expression in some parts but has mainly been focused on the conditions named in claims 6-10.

Box No. IV Lack of unity of invention

1. In response to the invitation to restrict or pay additional fees the applicant has:

- ☐ restricted the claims.
☐ paid additional fees.
☐ paid additional fees under protest.
☐ neither restricted nor paid additional fees.

2. ☒ This Authority found that the requirement of unity of invention is not complied with and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is:

- ☐ complied with.
☐ not complied with for the following reasons:

The compounds defined of the application have been divided into seven inventions according to the following:

1) Compounds according to formula I. Pharmaceutical formulations, use and methods involving these compounds and processes for the preparation of the compounds. Claims 1-17.

2) The compound 3-Amino-6-bromo- N- pyridin -3-ylpyrazine- 2-carboxamide and the use of this compound. Claims 18 and 26 partially.

3) The compounds

- 4- Bromo-N-[(1R)-2-hydroxy-1-methylethyl]benzenesulfonamide
4-Bromo-N-[(1R)-2-methoxy-1-methylethyl]benzenesulfonamide
4- Bromo-N-[(1S)-2-methoxy-1-methylethyl]benzenesulfonamide
4- Bromo-N-(1-ethyl-3-piperidinyl)benzenesulfonamide
4- Bromo-N,N-bis(2-methoxyethyl)benzenesulfonamide
4- bromo-N-(3-methylbutyl)benzenesulfonamide
4- bromo-N-(2-ethoxyethyl)benzenesulfonamide

and the use of these compounds. Claims 19 and 26 partially.

.../...

4. Consequently, this report has been established in respect of the following parts of the international application:

- ☐ all parts.
☒ the parts relating to claims Nos. 1-17

Supplemental Box

In case the space in any of the preceding boxes is not sufficient.

Continuation of: Box IV

4) The compounds

Methyl 3-amino-6-[4-(pyrrolidin-1-ylsulfonyl)phenyl]pyrazine-2-carboxylate

Methyl 3-amino-6-[4-[(4-methyl-1-piperazinyl)sulfonyl]phenyl]pyrazine-2-carboxylate

3-Amino-6-[4-[(4-methyl-1-piperazinyl)sulfonyl]phenyl]-2-pyrazincarboxylic acid

and the use of these compounds. Claims 20 and 26 partially.

5) The compounds

4-[(4-Methylpiperazine-1-yl)sulfonyl]phenylboronic acid

4-(Pyrrolidin-1-ylsulfonyl)phenylboronic acid

and the use of these compounds. Claims 21 and 26 partially

6) The compound

4-[2-(4-Bromo-2-fluorophenoxy)ethyl]morpholine and the use of this compound. Claims 22 and 26 partially.

7) Compounds comprising a polystyrene moiety (Formula XIX in the description) and the use of these compounds. Claims 23-24 and 26 partially.

8) The compound 4-{5-Amino-6-[(pyridin-3-ylamino)carbonyl]pyrazin-2-yl}benzoic acid and the use of this compound. Claims 25 and 26 partially.

Only invention I (claims 1-17) has been examined.

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**1. Statement**

| | | | |
|-------------------------------|--------|-----------------|-----|
| Novelty (N) | Claims | <u>1-10, 17</u> | YES |
| | Claims | | NO |
| Inventive step (IS) | Claims | <u>1-10, 17</u> | YES |
| | Claims | | NO |
| Industrial applicability (IA) | Claims | <u>1-10, 17</u> | YES |
| | Claims | | NO |

2. Citations and explanations (Rule 70.7)

The following documents are cited in the search report:

D1) WO 0168612 A2

D2) WO 03004472 A1 (published 16.01.2003)

The claimed invention relates to novel pyrazine-2-carboxamide derivatives, which have a selective inhibiting effect on glycogen synthase kinase 3 (GSK3) as well as a good bioavailability. The compounds can be used in the treatment of e.g. dementia, Alzheimer's Disease, chronic neurodegenerative diseases or diabetes.

D1 discloses aryl substituted pyrazine compounds, which can be used in the treatment of e.g. neurodegenerative and manic-depressive conditions.

The invention defined in claims 1-10 and 17 is not disclosed by this document.

The cited prior art does not give any indication that would lead a person skilled in the art to the claimed compounds which can be used in the treatment of e.g. dementia, Alzheimer's Disease, chronic neurodegenerative diseases or diabetes.

Therefore, the claimed invention is not obvious to a person skilled in the art.

Accordingly, the invention defined in claims 1-10 and 17 is novel and is considered to involve an inventive step. The invention is industrially applicable.

D2 discloses structurally close compounds with the use as the claimed compounds. Thus, D2 is published before the international filing date but before the claimed priority of the present application.

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Box No. VI Certain documents cited

1. Certain published documents (Rule 70.10)

| Application No. Patent No. | Publication date (day/month/year) | Filing date (day/month/year) | Priority date (valid claim) (day/month/year) |
|-------------------------------|--------------------------------------|---------------------------------|---|
| WO 03004472 | 16.01.2003 | 03.07.2002 | 05.07.2001 |

2. Non-written disclosures (Rule 70.9)

Kind of non-written disclosure

Date of non-written disclosure
(day/month/year)Date of written disclosure
referring to non-written disclosure
(day/month/year)